Claims

1. A controlled release pharmaceutical formulation comprising a rubbery matrix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active ingredient.

2. A formulation according to claim 1, wherein the active agent is an opioid, a stimulant, a barbiturate, an anti-depressant or a dissociative anaesthetic.

3. A formulation according to claim 2, wherein the active agent is oxycodone.

4. A formulation according to any preceding claim, which is resistant to tampering by reducing the release of the active agent upon extraction in a liquid which is water, ethanol or aqueous ethanol.

5. A formulation according to any preceding claim, which comprises multiparticulates.

6. A formulation according to any preceding claim, which shows at least one of the following characteristics (a) to (e) when tested by a test method comprising admixing a dosage amount of multiparticulates with 10 ml of the liquid in a glass flask and shaking at 500 to 600 oscillations per minute for 15 minutes using a Stuart Scientific Shaker Model SF1:

(a) 15 minutes shaking in water at room temperature: less than 7.5% release of active agent;

(b) 5 minutes standing in water at 50°C followed by 15 minutes shaking at the same temperature: less than 15% release of active agent;

(c) 5 minutes standing at 75°C followed by 15 minutes shaking at the same temperature: less than 20% release of active agent;

(d) 5 minutes standing at 100°C followed by 15 minutes shaking at the same temperature: less than 25% release of active agent;

(e) 15 minutes shaking in 40% ethanol at room temperature: preferably less than 25% release of active agent.

7. A formulation according to any preceding claim, wherein the tamper resistance reduces release of the active agent upon grinding of the formulation and extraction.

8. A formulation according to claim 7, which releases less than 10% of active agent when tested by a test method comprising subjecting a dosage amount of the formulation to grinding in a mortar and pestle with 24 rotations of the pestle and placing in 900 ml water at 37°C for 45 minutes.

9. A formulation according to claim 7, which releases less than 15% of active agent when tested by a test method comprising crushing a dosage amount in a pill pulverizer sold by Apex Healthcare Products,

and then extracting in 2 ml water heated to boiling on a spoon and filtering.

10. A formulation according to any preceding claim, wherein the matrix includes at least one other polymer to modify release.

11. A formulation according to claim 10, wherein the other polymer is an alkyl cellulose or a water insoluble ammonium methacrylate copolymer.

12. A formulation according to claim 11, wherein the other polymer is ethyl cellulose.

13. A formulation according to claim 12, wherein the amount of ethyl cellulose is 10 to 50% by weight of the formulation.

14. A formulation according to any of claims 10 to 13, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	15 to 50
active agent	5 to 55
other polymer to modify release	5 to 75
plasticiser	0 to 25
lubricant	0 to 25.

15. A formulation according to claim 14, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	20 to 45
active agent	5 to 50
other polymer to modify release	5 to 60
plasticiser	3 to 25
lubricant	0 to 20.

16. A formulation according to claim 14, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	25 to 45
active agent	10 to 45
other polymer to modify release	5 to 45
plasticiser	3 to 20
lubricant	0 to 15.

17. A formulation according to any preceding claim, which comprises up to 60% w/w of the active agent, 15 to 50% w/w of neutral poly(ethyl acrylate, methyl methacrylate) copolymer; 5 to 60% w/w of ethyl cellulose; and 7.5 to 20% of plasticiser.

18. A formulation according to claim 17, which further contains 5 to 60% of an insoluble ammonium methacrylate copolymer.

19. A formulation according to claim 18, which contains 35 to 50% of an insoluble ammonium methacrylate copolymer which is of low permeability and/or 5 to 30% of an ammonium methacrylate copolymer which is highly permeable.

20. A formulation according to any preceding claim, which contains a bulking agent.

21. A formulation according to any preceding claim, which contains an opioid and an opioid antagonist.

22. A formulation according to claim 21, which comprises 120 to 300 mg of oxycodone multiparticulates and 125 to 175 mg of oxycodone antagonist multiparticulates.

23. A formulation according to claim 21 or 22, which contains oxycodone and naltrexone.

24. A formulation according to claim 21, 22 or 23, which comprises melt extruded multiparticulates of an opioid and melt extruded multiparticulates of an opioid antagonist.

25. A unit dose of a pharmaceutical formulation according to any preceding claim suited for administration to a human.

26. A unit dose according to claim 25, which contains 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 120 mg or 160 mg of oxycodone.

27. A unit dose according to claim 25 or 26 suited for once a day dosing.

28. A unit dose form according to claim 27, which has an oxycodone dissolution rate *in vitro*, when measured by the USP Basket Method at 100 rpm in 900 ml aqueous buffer at a pH between 1.6 and 7.2 at 37°C of from 0% to about 40% at 1 hour, from about 8% to about 70% at 4 hours, from about 20% to about 80% at 8 hours, from about 30% to about 95% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 50% at 24 hours.

29. A unit dose according to claim 28, wherein the peak plasma level of oxycodone obtained *in vivo* occurs at 2 hours to 17 hours after administration of the dosage form.

30. A unit dose form according to claim 27, which has an oxycodone dissolution rate *in vitro*, when measured using the USP Basket Method <<7 11>> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37A unit dose form with detection by HPLC with UV at 206 nm wavelength; from 10 to 30% at 1 hour; from 20 to 35% at 2 hours; from 35 to 75%, at 8 hours; and greater than 50% at 16 hours.

31. A unit dose according to claim 25 or 26 suited for twice a day dosing.

32. A unit dose form according to claim 31 and which has an oxycodone dissolution rate *in vitro*, when measured by the USP Paddle Method (see the U.S. Pharmacopoeia XXII 1990) at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C of between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours.

33. A unit dose form according to claim 31 which has an oxycodone dissolution rate *in vitro*, when measured using the USP Basket Method << 7 11 >> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37°C with detection by HPLC with UV at 206 nm wavelength; of from 0 to 40% at 1 hour; from 20 to 70%, at 2 hours; from 40 to 80%, at 3 hours; from 60 to 95%, at 4 hours; and greater than 70% at 5 hours.

34. A unit dose according to claim 33, wherein the peak plasma level of oxycodone obtained *in vivo* occurs between 2 and 4.5 hours after administration of the dosage form.

35. A controlled release pharmaceutical formulation obtainable by melt extrusion and including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active ingredient.

36. A formulation according to claim 35, and which exhibits rubber-like characteristics.

37. A formulation according to claim 35 and 36 with enhanced resistance to tampering by extraction with water or alcohol or aqueous ethanol

38. A formulation according to claim 35, 36 or 37, wherein the active agent is an opioid, a stimulant, a barbiturate, an anti-depressant or a dissociative anaesthetic.

39. A formulation according to claim 38, wherein the active agent is oxycodone.

40. A formulation according to any of claims 35 to 39, which comprises multiparticulates.

41. A formulation according to any of claims 35 to 40, wherein the matrix includes at least one other polymer to modify release.

42. A formulation according to claim 41, wherein the other polymer is an alkyl cellulose or a water insoluble ammonium methacrylate copolymer.

43. A formulation according to claim 42, wherein the other polymer is ethyl cellulose.

44. A formulation according to claim 43, wherein the amount of ethyl cellulose is 10 to 50% by weight of the formulation.

45. A formulation according to any of claims 41 to 44, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	15 to 50
active agent	5 to 55
other polymer to modify release	5 to 75
plasticiser	0 to 25
lubricant	0 to 25.

46. A formulation according to claim 45, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	20 to 45
active agent	5 to 50
other polymer to modify release	5 to 60
plasticiser	3 to 25
lubricant	0 to 20.

47. A formulation according to claim 46, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	25 to 45
active agent	10 to 45

other polymer to modify release	5 to 45
plasticiser	3 to 20
lubricant	0 to 15.

48. A formulation according to any of claims 35 to 47, which comprises up to 60% w/w of the active agent, 15 to 50% w/w of neutral poly(ethyl acrylate, methyl methacrylate) copolymer; 5 to 60% w/w of ethyl cellulose; and 7.5 to 20% of plasticiser.

49. A formulation according to claim 48, which further contains 5 to 60% of an insoluble ammonium methacrylate copolymer.

50. A formulation according to claim 49, which contains 35 to 50% of an insoluble ammonium methacrylate copolymer which is of low permeability and/or 5 to 30% of an ammonium methacrylate copolymer which is highly permeable.

51. A formulation according to any of claims 35 to 50, which contains a bulking agent.

52. A formulation according to any of claims 35 to 50, which contains an opioid and an opioid antagonist.

53.A formulation according to claim 52, which comprises 120 to 300 mg of oxycodone multiparticulates and 125 to 175 mg of oxycodone antagonist multiparticulates.

54.A formulation according to claim 52 or 53, which contains oxycodone and naltrexone.

55.A formulation according to any of claims 52, 53 or 54, which comprises melt extruded multiparticulates of an opioid and melt extruded multiparticulates of an opioid antagonist.

56.A unit dose of a pharmaceutical formulation according to any of claims 35 to 55 suited for administration to a human.

57.A unit dose according to claim 56, which contains 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 120 mg or 160 mg of oxycodone.

58.A unit dose according to claim 56 or 57 suited for once a day dosing.

59.A unit dose form according to claim 58, which has an oxycodone dissolution rate *in vitro*, when measured by the USP Basket Method at 100 rpm in 900 ml aqueous buffer at a pH between 1.6 and 7.2 at 37°C of from 0% to about 40% at 1 hour, from about 8% to about 70% at 4 hours, from about 20% to

about 80% at 8 hours, from about 30% to about 95% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 50% at 24 hours.

60. A unit dose according to claim 58, wherein the peak plasma level of oxycodone obtained *in vivo* occurs at 2 hours to 17 hours after administration of the dosage form.

61. A unit dose form according to claim 58, which has an oxycodone dissolution rate *in vitro*, when measured using the USP Basket Method <<7 11>> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37° C with detection by HPLC with UV at 206 nm wavelength; from 10 to 30% at 1 hour; from 20 to 35% at 2 hours; from 35 to 75%, at 8 hours; and greater than 50% at 16 hours.

62. A unit dose according to claim 56 or 57 suited for twice a day dosing.

63. A unit dose form according to claim 62, which has an oxycodone dissolution rate *in vitro*, when measured by the USP Paddle Method (see the US Pharmacopoeia XXII 1990) at 100 rpm in 900ml aqueous buffer (p H between 1.6 and 7.2) at 37°C of between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt)

oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours.

64. A unit dose form according to claim 62 which has an oxycodone dissolution rate *in vitro*, when measured using the USP Basket Method << 7 11 >> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37°C with detection by HPLC with UV at 206 nm wavelength; of from 0 to 40% at 1 hour; from 20 to 70%, at 2 hours; from 40 to 80%, at 3 hours; from 60 to 95%, at 4 hours; and greater than 70% at 5 hours.

65. A unit dose according to claim 64, wherein the peak plasma level of oxycodone obtained *in vivo* occurs between 2 and 4.5 hours after administration of the dosage form.

66. A controlled release pharmaceutical formulation obtained by melt extrusion and including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active ingredient.

67. A dry granulate comprising a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an opioid analgesic.

68. A dry granulate comprising 20% to 66% by weight of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and a pharmaceutically active compound.

69.A dry granulate according to claim 68, wherein the pharmaceutically active compound is an opioid.

70.A dry granulate according to claim 69, wherein the opioid is oxyocodone or a salt thereof.

71.A dry granulate which comprises a matrix of the neutral poly(ethyl acrylate, methyl methacrylate) copolymer incorporating the opioid analgesic.

72.A dry granulate according to claim 71, which is an extruded granulate.

73.A dry granulate according to claim 71 or 72, which comprises up to 66% neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

74.A dry granulate according to claim 71, 72 or 73, which comprises 20 to 50% neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

75.A dry granulate according to claim 74, which comprises 30 to 40% neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

76. Multiparticulates each comprising a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an opioid analgesic.

77. Multiparticulates according to claim 76, formed by melt extrusion.

78. Multiparticulates according to claim 78, which take the form of a cylinder or are generally spherical, ellipsoidal or disc shaped.

79. Multiparticulates each comprising 20% to 66% by weight of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and a pharmaceutically active compound.

80. Multiparticulates according to claim 79, wherein the pharmaceutically active compound is an opioid analgesic.

81. Multiparticulates according to claim 80, wherein the opioid is oxycodone or a salt thereof.

82. Multiparticulates according to claim 80 and 81, formed by melt extrusion of a dry mix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

83. Multiparticulates according to claim 82, which take the form of a cylinder or are generally spherical, ellipsoidal or disc shaped.

84. A controlled release pharmaceutical formulation comprising a matrix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an opioid analgesic.

85. A controlled release pharmaceutical formulation comprising a matrix including 20% to 66% by weight of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and pharmaceutically active compound.

86. A formulation according to claim 85, and which exhibits rubber-like characteristics.

87. A formulation according to claim 85 or 86 with enhanced resistance to tampering by extraction with water or alcohol or aqueous ethanol

88. A formulation according to any of claims 84 to 87, wherein the opioid analgesic is oxycodone.

89. A formulation according to any of claims 84 to 88, which comprises multiparticulates.

90.A formulation according to any of claims 84 to 89, wherein the matrix includes at least one other polymer to modify release.

91.A formulation according to claim 90, wherein the other polymer is an alkyl cellulose or a water insoluble ammonium methacrylate copolymer.

92.A formulation according to claim 91, wherein the other polymer is ethyl cellulose.

93.A formulation according to claim 92, wherein the amount of ethyl cellulose is 10 to 50% by weight of the formulation.

94.A formulation according to claim 93, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	15 to 50
active agent	5 to 55
other polymer to modify release	5 to 75
Plasticiser	0 to 25
Lubricant	0 to 25.

95.A formulation according to claim 94, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	20 to 45
active agent	5 to 50
other polymer to modify release	5 to 60
Plasticiser	3 to 25
Lubricant	0 to 20.

96.A formulation according to claim 95, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	25 to 45
active agent	10 to 45
other polymer to modify release	5 to 45
Plasticiser	3 to 20
Lubricant	0 to 15.

97.A formulation according to any of claims 85 to 96, which comprises up to 60% w/w of the active agent, 15 to 50% w/w of neutral poly(ethyl acrylate, methyl methacrylate) copolymer; 5 to 60% w/w of ethyl cellulose; and 7.5 to 20% of plasticiser.

98.A formulation according to claim 97, which further contains 5 to 60% of an insoluble ammonium methacrylate copolymer.

99.A formulation according to claim 98, which contains 35 to 50% of an insoluble ammonium methacrylate copolymer which is of low permeability and/or 5 to 30% of an ammonium methacrylate copolymer which is highly permeable.

100. A formulation according to any of claims 85 to 99, which contains a bulking agent.

101. A formulation according to any of claims 85 to 100, which contains an opioid and an opioid antagonist.

102. A formulation according to claim 101, which comprises 120 to 300 mg of oxycodone multiparticulates and 125 to 175 mg of oxycodone antagonist multiparticulates.

103. A formulation according to claim 101 or 102, which contains oxycodone and naltrexone.

104. A formulation according to claim 101, 102 or 103, which comprises melt extruded multiparticulates of an opioid and melt extruded multiparticulates of an opioid antagonist.

105. A unit dose of a pharmaceutical formulation according to any of claims 87 to 104 suited for administration to a human.

106. A unit dose according to claim 105, which contains 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 120 mg or 160 mg of oxycodone.

107. A unit dose according to claim 105 or 106 suited for once a day dosing.

108. A unit dose form according to claim 107 which has an oxycodone dissolution rate *in vitro*, when measured by the USP Basket Method at 100 rpm in 900 ml aqueous buffer at a pH between 1.6 and 7.2 at 37°C of from 0% to about 40% at 1 hour, from about 8% to about 70% at 4 hours, from about 20% to about 80% at 8 hours, from about 30% to about 95% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 50% at 24 hours.

109. A unit dose according to claim 107, wherein the peak plasma level of oxycodone obtained *in vivo* occurs at 2 hours to 17 hours after administration of the dosage form.

110. A unit dose form according to claim 107, which has an oxycodone dissolution rate *in vitro*, when measured using the USP Basket Method <<7 11>> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37A unit dose form C with detection by HPLC with UV at 206 nm wavelength; from 10 to 30% at 1 hour; from 20 to 35% at 2 hours; from 35 to 75%, at 8 hours; and greater than 50% at 16 hours.

111. A unit dose according to claim 105 or 106 suited for twice a day dosing.

112. A unit dose form according to claim 111, which has an oxycodone dissolution rate *in vitro*, when measured by the USP Paddle Method (see the U.S. Pharmacopoeia XXII 1990) at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C of between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours.

113. A unit dose form according to claim 111 has an oxycodone dissolution rate *in vitro*, when measured using the USP Basket Method << 7 11 >> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37°C with detection by HPLC with UV at 206 nm wavelength; of from 0 to 40% at 1 hour; from 20 to 70%, at

2 hours; from 40 to 80%, at 3 hours; from 60 to 95%, at 4 hours; and greater than 70% at 5 hours.

114. A unit dose according to claim 113, wherein the peak plasma level of oxycodone obtained *in vivo* occurs between 2 and 4.5 hours after administration of the dosage form.

115. A process for preparing a controlled release formulation which comprises melt extrusion of a mix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active agent.

116. A process according to claim 115, wherein the neutral poly(ethyl acrylate, methyl methacrylate) copolymer is provided in the form of an aqueous dispersion comprising 40% of the polymer which is mixed with the active agent and dried to give the mix for melt extrusion.

117. A process according to claim 115 or 116, wherein the mix includes a plasticiser.

118. A process according to claim 117, wherein the plasticiser is tributyl citrate, stearyl alcohol or a high molecular weight polyethylene glycol.

119.A process according to any of claims 115 to 118 wherein the mix includes a lubricant.

120.A process according to claim 119, wherein the lubricant is stearic acid, a stearic acid salt, or glycerol dibehenate.

121.A process according to any of claims 115 to 120, which comprises wet granulation of the ingredients for the mix to be extruded to give a wet granulate, drying the granulate, and melt extrusion of the dried granulate.

122.A process according to claim 121, wherein the wet granulate is extruded before drying.

123.A process according to claim 122, wherein the dried granulate contains less than 3% w/w water.

124.A process according to any of claims 115 to 123, wherein the melt extrusion of the dry granulate is performed in a twin screw extruder.

125.A process according to any of claims 115 to 127, wherein extruded strands are conveyed to a pelletiser and cut to multiparticulates.

126.A process according to any of claims 115 to 125, wherein each multiparticulate has a dimaeter of about 1 mm and a length of about 1 mm.

127.A process according to any of claims 115 to 124, wherein a cutter cuts the extruded mix as it emerges from the extruder.

128.The use of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer in the preparation of a pharmaceutical formulation to provide resistance to tamper.

129.A method of imparting tamper resistance in a pharmaceutical formulation, which comprises admixing an active ingredient and a neutral poly(ethyl acrylate, methyl methacrylate) copolymer, and forming a pharmaceutical formulation incorporating the active ingredient in a matrix with the neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

130.A method of administration of an active ingredient, wherein the active ingredient is administered as a controlled release formulation according to any of claims 1 to 104.